Review

# Adult Stem Cell Therapy in Chronic Liver Diseases

**Young Woo Eom[1], Soon Koo Baik[1,2]**

[1]Cell Therapy and Tissue Engineering Center, Yonsei University, Wonju College of Medicine, Wonju, Korea
[2]Department of Internal Medicine, Yonsei University, Wonju College of Medicine, Wonju, Korea

The transplantation of mesenchymal stem cells (MSCs) represents a potentially effective therapy for chronic liver diseases. The potential of MSCs in the treatment of chronic liver disease is based on their ability to differentiate into multiple cell types including hepatocytes, their immunosuppressive properties, and their ability to secrete various trophic factors. This potential has been investigated in clinical and pre-clinical studies. Although the therapeutic mechanisms of MSC transplantation are still not fully characterized, accumulating evidence has revealed that various trophic factors secreted by MSCs play key therapeutic roles in regeneration. These trophic factors not only reduce inflammation, apoptosis, and fibrosis in damaged tissues but also stimulate angiogenesis and tissue regeneration in the impaired liver. In this review, we summarize the basic and therapeutic properties of MSCs, their therapeutic mechanisms of action, and potential transplantation routes for the treatment of chronic liver disease. We also discuss several risks associated with the use of MSCs in therapy, such as their fibrogenic potential and capacity to promote pre-existing tumor cell growth.

**Key Words:** Mesenchymal Stromal Cells; End Stage Liver Disease; Cell Transplantation; Liver Regeneration

Correspondence to: Soon Koo Baik
Department of Internal Medicine, Yonsei University, Wonju College of Medicine, 20 Ilsan-ro, Wonju 26426, Korea
Tel: +82-33-741-1223
Fax: +82-33-745-6782
E-mail: baiksk@yonsei.ac.kr

## INTRODUCTION

Chronic liver diseases (CLD) may result from viral hepatitis, alcohol and drug abuse, metabolic diseases and autoimmune attack. Such insults trigger hepatocyte apoptosis, impairment of the endothelial barrier, recruitment of inflammatory cells, and activation of hepatic stellate cells (HSCs), ultimately resulting in the onset of liver fibrosis [1,2]. Although liver transplantation is the only effective treatment for end-stage CLD, cell-based therapy has been proposed as a less invasive potential alternative to CLD. Several cells, including primary hepatocytes, unsorted bone marrow cells (BMCs), hematopoietic stem cells, and mesenchymal stem cells (MSCs), have the ability to improve liver function through replacement of damaged hepatocytes, inhibition of activated HSCs and regeneration of residual hepatocytes. Moreover, embryonic stem cells and induced pluripotent stem cells can differentiate into hepatocyte-like cells, making these useful in therapy to improve liver function [3,4].

### 1. Primary hepatocytes

The transplantation of primary hepatocytes represents a potential cell-based therapy for liver diseases, including metabolic disorders and acute liver failure [5]. However, human hepatocytes have been shown to be unsuitable as the availability of human livers as a source of cells is limited, and it is difficult to maintain hepatocyte viability and function during cryopreservation of the liver. In addition, hepatocytes are difficult to culture *in vitro* [6]. Moreover, while the safe transplantation of -5% of the total recipient liver cell mass (a maximum of $1–2 \times 10^8$ hepatocytes/body weight [kg]) has been demonstrated in human clinical trials [7], it has been reported that replacement of at least 10% of the hepatocellular mass is needed to compensate for missing or inactive proteins in genetic inborn errors of metabolism [8].

### 2. Unsorted bone marrow cells

The infusion of unsorted BMCs in patients with cirrhosis has been reported to be safe and feasible. Moreover, the infusion of

unsorted BMCs increases the serum albumin level and improves liver function [9]. However, although it has been reported that the infusion of unsorted BMCs elevates the levels of matrix metalloproteinases MMP-2, MMP-9, and MMP-14, reduces liver fibrosis, and improves survival rate [10], the therapeutic mechanism by which BMC infusion ameliorates liver damage remains unclear.

### 3. Hematopoietic stem cells

Hematopoietic stem cells from the bone marrow or peripheral blood, obtained by administration of G-CSF, which induces the mobilization of CD34+ cells into the peripheral blood, can be isolated, amplified, and differentiated into hepatocyte-like cells [11]. The infusion of hematopoietic stem cells improves serum albumin levels as well as Child-Pugh scores [12]. Although infused hematopoietic stem cells can differentiate into hepatocytes, through cell fusion or paracrine effects [13], further studies are necessary to define the role of hematopoietic stem cell therapy in liver disease patients.

### 4. Mesenchymal stem cells (MSCs)

MSCs can be isolated by plastic adherence from adipose tissue, brain, dermis, liver, lung, peripheral blood, skeletal muscle, umbilical cords, and cord blood [14,15]. MSCs are potentially useful therapeutic agents for the treatment of liver diseases, because of their potential to differentiate into hepatocytes, as well as their immunomodulatory properties and ability to secrete trophic factors. These properties, putative therapeutic mechanisms, and injection routes of MSCs are discussed in detail in a later section.

### 5. Embryonic stem cells (ESCs)

ESCs, which are isolated from the inner cell mass of blastocyst-stage embryos, have pluripotent differentiation potentials, including the ability to differentiate into hepatocyte-like cells. However, although ESCs have been shown to improve liver function in CCl4-treated mice [3], several issues are associated with their use, such as teratoma formation, ethical issues, and immune rejection problems [16].

### 6. Induced pluripotent stem cells (iPSCs)

The use of iPSCs, produced from patient-specific cells, allows ethical and immune rejection-related issues to be circumvented. IPSCs have been shown to differentiate into hepatocyte-like cells, and human iPSC-derived hepatocyte-like cells, from different ori-

gins, have been demonstrated to successfully repopulate liver tissue in mice with liver cirrhosis [4]. Although Liu H and colleagues reported that tumor formation was not observed in any organs of the transplanted mice, up to 7 months after transplantation of iPSC-derived hepatocyte-like cells [4], tumor formation must be carefully monitored, as an increased risk of teratoma formation is associated with the transplantation of these cells.

In this review, we focus only on MSCs, as these cells can be obtained in sufficient numbers for investigation in clinical studies, without ethical or immune rejection-related issues. We summarize the properties of MSCs, their therapeutic mechanisms of action, and injection routes, with the aim of providing an improved understanding of the potential of MSCs in regenerative medicine, including the treatment of liver disease.

## PROPERTIES OF MESENCHYMAL STEM CELLS

MSCs are adult stem cells that have been used for cell-based tissue engineering and regenerative medicine. The safety and efficacy of MSCs in regenerative medicine have been evaluated in clinical trials for cardiovascular, neurological, and immunological diseases, with encouraging results [17-19]. The minimal criteria for human MSCs were defined by the International Society for Cellular Therapy in 2006, as follows: 1) MSCs must be plastic-adherent when maintained under standard culture conditions. 2) More than 95% of cells in a given population of MSCs should express CD105, CD73 and CD90, and lack the expression (less than 2% positive) of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA class II surface molecules. 3) MSCs must differentiate into osteoblasts, adipocytes, and chondroblasts under standard conditions *in vitro* [20].

The properties of MSCs discussed here include their basic characteristics as stem cells, and the properties that define their therapeutic potential. With regard to their basic characteristics as stem cells, MSCs can proliferate to reach sufficient cell numbers for clinical studies (self-renewal), and differentiate into multiple cell lineages, including hepatocytes. However, the stemness of MSCs, which is defined by their potential to proliferate and differentiate, gradually decreases during serial passages that are required to obtain sufficient cell numbers for clinical studies. Therefore, regulation of stemness in MSCs is crucial for achievement of their potential in stem cell therapy, for tissue engineering and regenerative medicine. Although it has been considered that the therapeutic

properties of MSCs relevant to CLD are related to their capacity for hepatocyte-like differentiation, trans-differentiation of MSCs into hepatocytes was rarely observed in animal models injected with MSCs. Their ability to migrate into damaged sites, secrete trophic factors, and exert immunosuppressive, antifibrotic, and antioxidant effects is recognized as the basis of their therapeutic potential in regenerative medicine, particularly for the treatment of CLDs.

## THERAPEUTIC MECHANISMS OF MESENCHYMAL STEM CELLS IN THE TREATMENT OF CHRONIC LIVER DISEASES

### 1. Hepatocyte-like differentiation of mesenchymal stem cells

MSCs exposed to growth factors and cytokines (i.e. hepatocyte growth factor [HGF], fibroblast growth factor [FGF]-2/-4, epidermal growth factor [EGF], oncostatin M [OSM], and/or leukemia inhibitory factor [LIF]), and chemical compounds (i.e. dexamethasone [Dex], insulin-transferrin-selenium [ITS], and/or nicotinamide [NTA]) can differentiate into hepatocyte-like cells, which express HNF-3, GATA4, CK19, transthyretin, -fetoprotein, albumin, and CK18 [21]. Hepatocyte-like differentiation of MSCs can also be induced by co-culture with liver cells [22] and by pellet culture [23]. Additionally, *in vivo* hepatic differentiation of MSCs was achieved in allylalcohol (AA)–treated rat livers, by directly xenografting human bone marrow-derived MSCs into these AA-treated rat livers, resulting in most of the human MSCs differentiating into hepatocyte-like cells without fusion, as revealed by positive immunostaining for human specific AFP, albumin, CK19, CK18, and receptor [24]. Although hepatic-differentiated MSCs exhibit hepatocyte-specific cuboidal morphology and express hepatocyte marker genes *in vitro* and *in vivo*, it is still debatable as to whether transplanted MSCs can completely regenerate hepatocytes *in vivo*. As trans-differentiation of MSCs into hepatocytes is rarely observed (less than 1% of the total liver mass) in animal models, recently published data suggest that the therapeutic potential of MSCs in the treatment of CLDs would be primarily based on their ability to secrete trophic factors, and their immunosuppressive effects, rather than trans-differentiation into hepatocytes [25,26].

### 2. Migration of mesenchymal stem cells

MSCs migrate towards damaged areas in response to homing signals. Many studies have shown that MSCs are able to migrate to injured tissues from blood, and exert therapeutic effects at these sites of injury [27]. Various factors, such as chemokines, cytokines, and growth factors, released upon injury, play roles as migratory cues for systemically or locally transplanted MSCs [28]. Specific receptors and ligands that are upregulated in injured tissues facilitate trafficking, adhesion, and infiltration of MSCs at sites of injury [27]. Moreover, these tissues provide MSCs with the appropriate microenvironment for self-renewal and maintenance of multi-potentiality [27]. Integrins, selectins, and chemokine receptors [29] expressed on MSCs play key roles in their migration across the endothelium. In addition, MSCs are passively arrested in capillaries or microvessels, including arterioles and post-capillary venules, where they interact directly with accessory cells and release a wide array of soluble growth factors and trophic cytokines [30].

### 3. Immunosuppressive potential of mesenchymal stem cells

MSCs can suppress immune cells, such as B-cells, T-cells, dendritic cells (DCs), and natural killer cells (NKs) and promote the generation of regulatory T (Tregs) cells through the production of soluble factors such as nitric oxide (NO), prostaglandin (PGE2), indoleamine 2,3-dioxygenase (IDO), IL-6, IL-10, and human leukocyte antigen (HLA)-G [31]. The production of NO by inducible nitric-oxide synthase (iNOS) in murine MSCs is suggested to play a major role in T-cell proliferation inhibition [32]. PGE2 acts as a powerful immunosuppressant, modulating production of IL-10, proliferation, and differentiation of T-cells, macrophages, and monocytes, respectively [33,34]. Moreover, IDO and HLA-G suppress the proliferation of B- and effector T-cells, inhibit the maturation of DCs, and reduce the cytotoxicity of natural killer (NK) cells.

In addition to immunosuppression mediated by the secretion of soluble factors, MSCs can make direct contact with immune cells, thereby suppressing their activation. MSCs can inhibit T-cell proliferation by inducing apoptosis of effector T-cells, through engagement of programmed death 1 (PD-1) protein to its ligands. The complexes, PD-L1 and PD-L2, thus formed are able to render T-cells anergic by downregulating the expression of co-stimulatory molecules CD80 and CD86 on antigen presenting cells [35].

The immune-privileged status of the liver can be disrupted by unbalanced immune cell populations, or immune cell infiltration into the liver, resulting in liver injury. Therefore, the immunosuppressive potential of MSCs plays an important role in the treatment of CLDs.

### 4. Secretion of trophic factors in mesenchymal stem cells

Various trophic factors can play important therapeutic roles in regenerative medicine. MSCs express various trophic factors, such as growth factors (i.e. brain-derived neurotrophic factor [BDNF], EGF, FGF-2, FGF-4, FGF-7, FGF-9, and FGF-17, glial cell-derived neurotrophic factor [GDNF], HGF, insulin-like growth factor [IGF]-1, nerve growth factor [NGF], platelet-derived growth factor [PD-GF], and vascular endothelial growth factor [VEGF]), cytokines (i.e IFN-γ, IL-1α, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12, and IL-13, TNF-α, and transforming growth factor [TGF]-β), and chemokines (i.e. various C-C motif ligand [CCLs], and C-X-C motif ligand [CXCLs]), which are known to not only reduce inflammation, apoptosis, and fibrosis of damaged tissues, but also stimulate angiogenesis and regeneration of injured cells [36]. These trophic factors, which are stimulated by local signals from damaged sites, such as inflammatory cytokines, ligands of Toll-like receptors, and hypoxia, modify the local environment in the liver [37], and facilitate the survival of living and dying hepatocytes via anti-apoptotic factors (i.e. stromal cell-derived factor [SDF]-1, HGF, IGF-1, and VEGF), mitogens (i.e. EGF, HGF, NGF, and TGF-α), and angiogenic factors (i.e. VEGF) [38].

### 5. Anti-fibrotic activities of mesenchymal stem cells

After damage of healthy tissue, the repair process started to replace dead and damaged cells and then lead to substantial remodeling of the extracellular matrix (ECM), known as fibrosis. During liver fibrosis, HSCs are responsible for deposition of ECM proteins in liver. The anti-fibrotic activities of MSCs have been reported in various fibrotic animal models including heart, liver, kidneys, lungs, peritoneum, pancreas, skin, and rectum. The molecular mechanism underlying the anti-fibrotic properties of MSCs can mainly reside in the high expression levels of matrix metalloproteinases (MMPs), especially MMP-9, which may directly degrade the extracellular matrix and lead to apoptosis of HSCs [39]. In several fibrosis models, MSCs have been shown to increase the expression of MMPs (i.e., MMP-2, MMP-9, MMP-13, and MMP-14) [40] or to decrease tissue inhibitors of MMPs (TIMP)-1 expression [41], and these alterations are generally associated with resolution of fibrosis. Moreover, MSCs can alleviate the chronic inflammation via their immunosuppressive properties and then diminish tissue fibrosis. MSCs can also suppress the proliferation of activated HSCs and collagen synthesis through indirect or direct cell-cell contact models [42].

### 6. Anti-oxidant activities of mesenchymal stem cells

Excessive reactive oxygen species (ROS) induces liver diseases such as liver fibrosis, cirrhosis, viral hepatitis, hepatocellular carcinoma (HCC) and others through oxidative disease [43]. Carbon tetrachloride (CCl4) and thioacetamide (TAA) are toxins used to generate liver injury in animal models [44]. These toxins stimulate ROS production, which result in hepatocyte damage through lipid peroxidation and the alkylation of proteins, nucleic acids, and lipids [44,45]. MSCs have been shown to overcome CCL4- and TAA-induced oxidative stress *in vitro* and to reduce liver injury through anti-oxidant activities *in vivo* [44,46]. The upregulation of ROS in CCl4-treated liver cells has been reported to be attenuated by co-culturing with MSCs via an increase in superoxide dismutase (SOD) activity and the induction of AREs, which represents a cytoprotective response in the injured liver [44]. Additionally, MSCs protect hepatocytes by reducing ROS damage that is induced by TAA both *in vivo* and *in vitro* [46].

## TRANSPLANTATION ROUTE OF MESENCHYMAL STEM CELLS

MSCs communicate with other cells in the body and migrate toward damaged tissue in response to homing signals. Chemotactic SDF-1α, secreted at injury sites, plays a key role in the migration of MSCs expressing C-X-C chemokine receptor type 4 (CXCR4), the CXCR4-SDF-1α axis [47]. Based on this migratory property of MSCs, intravenous, intraperitoneal, intrahepatic, intrasplenic, or portal-venous injections have been shown to deliver MSCs to the liver, although the reported effectiveness has differed slightly based on the injection route and the study involved [26,48]. Baertschiger et al. observed that stable engraftment of MSCs in the liver could not be achieved following intrasplenic injection. It was observed that, following intrahepatic injection in the acute liver injury animal model, MSCs permanently remained in the liver, but primarily differentiated into myofibroblasts, which expressed vimentin and α-SMA but not hepatic markers [49]. Therefore, the MSC transplantation route used should be taken into consideration for enhancement of stable engraftment, and reduction of the fibrogenic effects of MSCs.

## FUTURE PERSPECTIVES

Although MSCs have been widely used in clinical and pre-clini-

cal studies of CLD treatments, further studies are needed to resolve various issues, such as those relating to the fibrogenic potential of MSCs, and their ability to promote pre-existing tumor cell growth. MSCs injected into non-obese diabetic severe combined immunodeficient (NOD/SCID) mice with liver injury could be differentiated into myofibroblasts, rather than into hepatocytes, according to MSC injection route and disease status of the mice [49,50]. Liver engraftment of human MSCs was very low in normal and acutely injured NOD/SCID mice, while significantly higher numbers of human MSCs were found in chronically injured livers. Moreover, a significant number of human MSCs exhibited a myofibroblast-like morphology during acute liver injury [50]. In addition to the fibrogenic potential of MSCs to undergo malignant transformation during ex-vivo expansion, MSCs are able to promote the growth of pre-existing tumors, through the secretion of growth factors. Although malignant transformation of human MSCs has not been reported in clinical trials, MSCs must be carefully screened for deleterious genetic mutations prior to their transplantation.

## CONCLUSIONS

MSCs treatments are considered to be generally safe, and may serve as a potential therapeutic agent to improve liver function in patients with CLD, because of their differentiation potential into hepatocyte-like cells, their immunosuppressive properties, and secretion of various trophic factors promoting liver regeneration. Nevertheless, several issues, including those that involve the fibrogenic potential of MSCs and their ability to promote pre-existing tumor cell growth, must be carefully considered.

## REFERENCES

1. Ghatak S, Biswas A, Dhali GK, Chowdhury A, Boyer JL, Santra A. Oxidative stress and hepatic stellate cell activation are key events in arsenic induced liver fibrosis in mice. Toxicol Appl Pharmacol 2011;251:59-69.
2. Malhi H, Gores GJ. Cellular and molecular mechanisms of liver injury. Gastroenterology 2008;134:1641-54.
3. Yamamoto H, Quinn G, Asari A, Yamanokuchi H, Teratani T, Terada M, et al. Differentiation of embryonic stem cells into hepatocytes: biological functions and therapeutic application. Hepatology 2003;37:983-93.
4. Liu H, Kim Y, Sharkis S, Marchionni L, Jang YY. In vivo liver regeneration potential of human induced pluripotent stem cells from diverse origins. Sci Transl Med 2011;3:82ra39.
5. Sokal EM, Smets F, Bourgois A, Van Maldergem L, Buts JP, Reding R, et al. Hepatocyte transplantation in a 4-year-old girl with peroxisomal biogenesis disease: technique, safety, and metabolic follow-up. Transplanta-
tion 2003;76:735-8.
6. Stephenne X, Najimi M, Ngoc DK, Smets F, Hue L, Guigas B, et al. Cryopreservation of human hepatocytes alters the mitochondrial respiratory chain complex 1. Cell Transplant 2007;16:409-19.
7. Puppi J, Tan N, Mitry RR, Hughes RD, Lehec S, Mieli-Vergani G, et al. Hepatocyte transplantation followed by auxiliary liver transplantation--a novel treatment for ornithine transcarbamylase deficiency. Am J Transplant 2008;8:452-7.
8. Asonuma K, Gilbert JC, Stein JE, Takeda T, Vacanti JP. Quantitation of transplanted hepatic mass necessary to cure the Gunn rat model of hyperbilirubinemia. J Pediatr Surg 1992;27:298-301.
9. Terai S, Tanimoto H, Maeda M, Zaitsu J, Hisanaga T, Iwamoto T, et al. Timeline for development of autologous bone marrow infusion (ABMi) therapy and perspective for future stem cell therapy. J Gastroenterol 2012; 47:491-7.
10. Sakaida I, Terai S, Nishina H, Okita K. Development of cell therapy using autologous bone marrow cells for liver cirrhosis. Med Mol Morphol 2005; 38:197-202.
11. Salama H, Zekri AR, Zern M, Bahnassy A, Loutfy S, Shalaby S, et al. Autologous hematopoietic stem cell transplantation in 48 patients with end-stage chronic liver diseases. Cell Transplant 2010;19:1475-86.
12. Pai M, Zacharoulis D, Milicevic MN, Helmy S, Jiao LR, Levicar N, et al. Autologous infusion of expanded mobilized adult bone marrow-derived CD34+ cells into patients with alcoholic liver cirrhosis. Am J Gastroenterol 2008;103:1952-8.
13. Vassilopoulos G, Wang PR, Russell DW. Transplanted bone marrow regenerates liver by cell fusion. Nature 2003;422:901-4.
14. Campagnoli C, Roberts IA, Kumar S, Bennett PR, Bellantuono I, Fisk NM. Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver, and bone marrow. Blood 2001;98:2396-402.
15. Young HE, Steele TA, Bray RA, Hudson J, Floyd JA, Hawkins K, et al. Human reserve pluripotent mesenchymal stem cells are present in the connective tissues of skeletal muscle and dermis derived from fetal, adult, and geriatric donors. Anat Rec 2001;264:51-62.
16. Gilchrist ES, Plevris JN. Bone marrow-derived stem cells in liver repair: 10 years down the line. Liver Transpl 2010;16:118-29.
17. Lee PH, Kim JW, Bang OY, Ahn YH, Joo IS, Huh K. Autologous mesenchymal stem cell therapy delays the progression of neurological deficits in patients with multiple system atrophy. Clin Pharmacol Ther 2008;83: 723-30.
18. Ringden O, Uzunel M, Rasmusson I, Remberger M, Sundberg B, Lonnies H, et al. Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease. Transplantation 2006;81:1390-7.
19. Ripa RS, Haack-Sorensen M, Wang Y, Jorgensen E, Mortensen S, Bindslev L, et al. Bone marrow derived mesenchymal cell mobilization by granulocyte-colony stimulating factor after acute myocardial infarction: results from the Stem Cells in Myocardial Infarction (STEMMI) trial. Circulation 2007;116:I24-30.
20. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006;8:315-7.
21. Schwartz RE, Reyes M, Koodie L, Jiang Y, Blackstad M, Lund T, et al. Multipotent adult progenitor cells from bone marrow differentiate into functional hepatocyte-like cells. J Clin Invest 2002;109:1291-302.
22. Lange C, Bassler P, Lioznov MV, Bruns H, Kluth D, Zander AR, et al. Liver-specific gene expression in mesenchymal stem cells is induced by liver cells. World J Gastroenterol 2005;11:4497-504.
23. Ong SY, Dai H, Leong KW. Inducing hepatic differentiation of human

mesenchymal stem cells in pellet culture. Biomaterials 2006;27:4087-97.

24. Sato Y, Araki H, Kato J, Nakamura K, Kawano Y, Kobune M, et al. Human mesenchymal stem cells xenografted directly to rat liver are differentiated into human hepatocytes without fusion. Blood 2005;106:756-63.

25. Xagorari A, Siotou E, Yiangou M, Tsolaki E, Bougiouklis D, Sakkas L, et al. Protective effect of mesenchymal stem cell-conditioned medium on hepatic cell apoptosis after acute liver injury. Int J Clin Exp Pathol 2013;6:831-40.

26. Jang YO, Kim YJ, Baik SK, Kim MY, Eom YW, Cho MY, et al. Histological improvement following administration of autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: a pilot study. Liver Int 2014;34:33-41.

27. Chapel A, Bertho JM, Bensidhoum M, Fouillard L, Young RG, Frick J, et al. Mesenchymal stem cells home to injured tissues when co-infused with hematopoietic cells to treat a radiation-induced multi-organ failure syndrome. J Gene Med 2003;5:1028-38.

28. Sordi V, Malosio ML, Marchesi F, Mercalli A, Melzi R, Giordano T, et al. Bone marrow mesenchymal stem cells express a restricted set of functionally active chemokine receptors capable of promoting migration to pancreatic islets. Blood 2005;106:419-27.

29. Brooke G, Tong H, Levesque JP, Atkinson K. Molecular trafficking mechanisms of multipotent mesenchymal stem cells derived from human bone marrow and placenta. Stem Cells Dev 2008;17:929-40.

30. Cselenyak A, Pankotai E, Horvath EM, Kiss L, Lacza Z. Mesenchymal stem cells rescue cardiomyoblasts from cell death in an in vitro ischemia model via direct cell-to-cell connections. BMC Cell Biol 2010;11:29.

31. Ghannam S, Bouffi C, Djouad F, Jorgensen C, Noel D. Immunosuppression by mesenchymal stem cells: mechanisms and clinical applications. Stem Cell Res Ther 2010;1:2.

32. Sato K, Ozaki K, Oh I, Meguro A, Hatanaka K, Nagai T, et al. Nitric oxide plays a critical role in suppression of T-cell proliferation by mesenchymal stem cells. Blood 2007;109:228-34.

33. Nemeth K, Leelahavanichkul A, Yuen PS, Mayer B, Parmelee A, Doi K, et al. Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. Nat Med 2009;15:42-9.

34. Spaggiari GM, Abdelrazik H, Becchetti F, Moretta L. MSCs inhibit monocyte-derived DC maturation and function by selectively interfering with the generation of immature DCs: central role of MSC-derived prostaglandin E2. Blood 2009;113:6576-83.

35. Augello A, Tasso R, Negrini SM, Amateis A, Indiveri F, Cancedda R, et al. Bone marrow mesenchymal progenitor cells inhibit lymphocyte proliferation by activation of the programmed death 1 pathway. Eur J Immunol 2005;35:1482-90.

36. Kupcova Skalnikova H. Proteomic techniques for characterisation of mesenchymal stem cell secretome. Biochimie 2013;95:2196-211.

37. Caplan AI, Dennis JE. Mesenchymal stem cells as trophic mediators. J Cell Biochem 2006;98:1076-84.

38. Wang L, Wang X, Wang L, Chiu JD, van de Ven G, Gaarde WA, et al. Hepatic vascular endothelial growth factor regulates recruitment of rat liver sinusoidal endothelial cell progenitor cells. Gastroenterology 2012;143:1555-63. e2.

39. Higashiyama R, Inagaki Y, Hong YY, Kushida M, Nakao S, Niioka M, et al. Bone marrow-derived cells express matrix metalloproteinases and contribute to regression of liver fibrosis in mice. Hepatology 2007;45:213-22.

40. Rabani V, Shahsavani M, Gharavi M, Piryaei A, Azhdari Z, Baharvand H. Mesenchymal stem cell infusion therapy in a carbon tetrachloride-induced liver fibrosis model affects matrix metalloproteinase expression. Cell Biol Int 2010;34:601-5.

41. Ali G, Mohsin S, Khan M, Nasir GA, Shams S, Khan SN, et al. Nitric oxide augments mesenchymal stem cell ability to repair liver fibrosis. J Transl Med 2012;10:75.

42. Wang J, Bian C, Liao L, Zhu Y, Li J, Zeng L, et al. Inhibition of hepatic stellate cells proliferation by mesenchymal stem cells and the possible mechanisms. Hepatol Res 2009;39:1219-28.

43. Cash WJ, McCance DR, Young IS, McEneny J, Cadden IS, McDougall NI, et al. Primary biliary cirrhosis is associated with oxidative stress and endothelial dysfunction but not increased cardiovascular risk. Hepatol Res 2010;40:1098-106.

44. Cho KA, Woo SY, Seoh JY, Han HS, Ryu KH. Mesenchymal stem cells restore CCl4-induced liver injury by an antioxidative process. Cell Biol Int 2012;36:1267-74.

45. Parola M, Robino G. Oxidative stress-related molecules and liver fibrosis. J Hepatol 2001;35:297-306.

46. Quintanilha LF, Takami T, Hirose Y, Fujisawa K, Murata Y, Yamamoto N, et al. Canine mesenchymal stem cells show antioxidant properties against thioacetamide-induced liver injury in vitro and in vivo. Hepatol Res 2014;44:E206-17.

47. Karp JM, Leng Teo GS. Mesenchymal stem cell homing: the devil is in the details. Cell Stem Cell 2009;4:206-16.

48. Kharaziha P, Hellstrom PM, Noorinayer B, Farzaneh F, Aghajani K, Jafari F, et al. Improvement of liver function in liver cirrhosis patients after autologous mesenchymal stem cell injection: a phase I-II clinical trial. Eur J Gastroenterol Hepatol 2009;21:1199-205.

49. Baertschiger RM, Serre-Beinier V, Morel P, Bosco D, Peyrou M, Clement S, et al. Fibrogenic potential of human multipotent mesenchymal stromal cells in injured liver. PLoS One 2009;4:e6657.

50. di Bonzo LV, Ferrero I, Cravanzola C, Mareschi K, Rustichell D, Novo E, et al. Human mesenchymal stem cells as a two-edged sword in hepatic regenerative medicine: engraftment and hepatocyte differentiation versus profibrogenic potential. Gut 2008;57:223-31.